Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)
Journal Impact Factor® (2024): 2.2
CiteScore® (2024): 5.2
www.biomolbiomed.com | blog.bjbms.org

RESEARCH ARTICLE

Cho et al: Dantrolene use in clinical practice

Dantrolene use across surgical and medical care at Mayo Clinic from 2010 to 2024: Indications, frequency, and value for identifying malignant hyperthermia

David Cho[1], Toby N. Weingarten[2], Juraj Sprung[2], Aurelia Zodl[2], Martin J. Ryll[2], Tracy E. Harrison[2*]

[1]Mayo Clinic Alix School of Medicine, Rochester, Minnesota, USA;

[2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA.

*Correspondence to Tracy E. Harrison: harrison.tracy@mayo.edu.

DOI: https://doi.org/10.17305/bb.2025.13340

ABSTRACT

Dantrolene is the definitive treatment for malignant hyperthermia (MH), a rare and life-threatening disorder. This retrospective study aimed to achieve two objectives: (1) to characterize the indications and frequency of dantrolene administration in both medical and surgical settings, and (2) to evaluate whether perioperative dantrolene may serve as a surrogate marker for identifying MH cases. Using pharmacy records, we identified hospitalized patients who received dantrolene between 2010 and 2024. Each recipient underwent a chart review to examine the clinical context of dantrolene administration. A total of 1,199,450 inpatient pharmacy records were reviewed, revealing 118 patients who received dantrolene, resulting in an incidence rate of 1 in 10,165 hospital admissions (95% CI: 1 in 8,488 to 1 in 12,280). Among these, 87 patients (74%) received oral dantrolene: 84 for chronic spasticity, two for neuroleptic malignant syndrome, and one as preoperative prophylaxis due to a history of MH. The remaining 31 patients (26%) received intravenous dantrolene. Seventeen patients received perioperative dantrolene for suspected MH; of these, nine cases (53%) were subsequently clinically confirmed as MH. Based on these findings and the total number of surgical procedures involving general anesthesia (*n*=885,127), the estimated prevalence of MH following general anesthesia was calculated to be 1 in 98,328 exposures (95% CI: 1 in 51,813 to 1 in 215,054). Dantrolene was administered at an approximate rate of 1 per 10,000 hospital admissions, primarily in oral formulation for chronic spasticity. Among the patients who received perioperative dantrolene, approximately half were confirmed to have MH, resulting in an estimated MH prevalence of 1 in 100,000 patients exposed to general anesthesia.

Keywords: Dantrolene, malignant hyperthermia, surrogate marker, general anesthesia.

INTRODUCTION

Dantrolene, a direct-acting skeletal muscle relaxant, is infrequently used in general clinical practice. It is occasionally prescribed for conditions associated with muscle spasticity, including spinal cord injury, stroke, multiple sclerosis, and cerebral palsy. Additionally, dantrolene plays a major role in the management of several emergent conditions, such as malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS), tetanus, serotonin syndrome, heat stroke, and catecholaminergic polymorphic ventricular tachycardia. In the surgical setting, dantrolene is recognized as the only and specific first-line treatment for MH.

MH is a rare, life-threatening hypermetabolic reaction which typically occurs in the perioperative setting and is inherited in an autosomal dominant pattern. It is caused by uncontrolled calcium (Ca^{2+}) release from the sarcoplasmic reticulum (SR) through mutated ryanodine type 1 receptor (RYR1) Ca^{2+} channel [1]. RYR1 is located on the SR membrane of skeletal muscle cells. In individuals with MH susceptibility (i.e., with mutations in the *RYR1* gene) a fulminant hyperthermic crisis can be triggered by exposure to volatile anesthetic agents (sevoflurane, desflurane, isoflurane) or depolarizing muscle relaxant (succinylcholine). In MH-susceptible patients, the mutated RYR1 Ca^{2+} channel fails to close leading to excessive Ca^{2+} release into the cytosol of muscle cells. This Ca^{2+} overload leads to sustained skeletal muscle contraction (muscle rigidity), myofibrillar disruption (rhabdomyolysis), increased carbon dioxide production (hypercapnia and respiratory acidosis), metabolic acidosis, and potentially fatal hyperthermic reaction. By inhibiting Ca^{2+} release through the RYR1 channel, dantrolene limits cross-bridge formation between actin and myosin, reduces skeletal muscle contraction and abolishes the hypermetabolic crisis.

Intravenous (IV) dantrolene use typically indicates an urgent clinical situation. Since it is a highly specific treatment for malignant hyperthermia (MH) with few alternative uses, its administration in perioperative setting can serve as a proxy for MH [2, 3]. In this study, we reviewed the Mayo Clinic Rochester hospital pharmacy records spanning 14.5 years to identify patients who received IV or peroral dantrolene (PO), representing a diverse population across both surgical and medical settings. Our primary aim was to assess the frequency and clinical indications for dantrolene use in hospitalized

patients. We also evaluated how accurately perioperative IV dantrolene identified MH to help estimate its perioperative prevalence.

MATERIALS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board (identification number: 24-007824, approved October 7, 2024). Consistent with Minnesota Statute 144.295, patients who declined prior written authorization for their medical records to be used in research were excluded from this study. This manuscript adheres to the applicable STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [4].

Study design

This retrospective study was conducted at Mayo Clinic Hospital, Rochester Minnesota, a quaternary academic medical center. Each hospital admission generates a corresponding pharmacy record; therefore, the number of pharmacy records is equivalent to the number of hospital admissions (inpatient and outpatient). Pharmacy records for inpatients were reviewed for the period from January 1, 2010, to June 30, 2024, to identify patients who received dantrolene. During the same time frame, data from the Mayo Clinic Anesthesia Database were used to determine the number of patients who received general anesthesia, regional anesthesia, and monitored anesthesia care for both inpatients and outpatients.

For patients who received dantrolene, medical records were reviewed to determine the intended indication for its use. For those who received IV dantrolene intraoperatively or in the immediate postoperative period, we examined the type of anesthetic management and documented the anesthetic agents used. Clinical presentations, treatments, and outcomes were further analyzed. When available, the final clinical diagnosis was recorded; if a definitive diagnosis was not established, we documented the differential diagnosis as noted in the medical records. Descriptive statistics were used for data analysis. We report on the prevalence of dantrolene administration across medical and surgical in-patient population, with a primary focus on surgical patients to determine the prevalence of MH.

RESULTS

Indications for dantrolene administration

Between January 1, 2010, and June 30, 2024, a total of 1,199,450 pharmacy records for inpatient hospital admissions were reviewed to detect those who received dantrolene. During this period, we identified 118 patients who received dantrolene (estimated rate of 1 in 10,165 hospital admissions; 95% CI: 1:8,488 to 1:12,280). Dantrolene was administered orally to 87 patients (73.4%): 84 for chronic spasticity, two for suspected NMS, and one as preoperative prophylaxis in a patient with a known history of MH. The remaining 31 patients (26.3%) received IV dantrolene: 17 in the perioperative setting and 14 outside the perioperative setting (Supplementary Table 1).

Prevalence of MH in surgical population

During the study period, 1,317,411 patients received anesthetic care from our department for both inpatient and outpatient procedures. Of these, 885,127 underwent general anesthesia, 76,282 regional anesthesia, and 365,002 monitored anesthetic care. Seventeen patients were administered IV dantrolene in the perioperative setting. Of these, nine were diagnosed with MH; all associated with triggering agents during general anesthesia (Table 1). Four of these nine had genetic testing, all of which found a *RYR1* variant associated with MH susceptibility.

An additional eight patients presented with an MH-like clinical picture, but were subsequently diagnosed with other conditions, including sepsis, neuroleptic malignant syndrome, or serotonin syndrome (Table 2). Based on confirmed MH cases, the estimated prevalence of MH was 1 in 98,347 exposures to general anesthesia (95% CI: 1:51,808 to 1:215,078). Notably, four MH patients had multiple prior uneventful exposures to volatile anesthetics, two had previously undergone uneventful procedures under total intravenous anesthesia, and three had no prior anesthesia exposure.

Prevalence of MH in surgical population

During the study period, 952,985 patients underwent procedures with anesthesia, and 9 were confirmed with MH: 885,127 had general anesthesia, 76,282 regional anesthesia, and 356,002 monitored anesthesia care. All 9 MH cases occurred in

association with exposure to general anesthesia with MH-triggering agents. The estimated prevalence of MH in the perioperative period was 1 in 98,328 general anesthetics (95% CI: 1 in 51,813 to 1 in 215,054). Notably, four MH patients had multiple prior uneventful exposures to volatile anesthetics, two underwent prior uneventful procedures under total intravenous anesthetics, and three had no prior anesthesia exposure.

Clinical characteristics of MH cases

Among the nine patients diagnosed with MH, four underwent genetic sequencing and were found to have a heterozygous mutation in the *RYR1* gene, while the remaining five were diagnosed with MH based on clinical criteria. All nine received a volatile anesthetic, and four also received succinylcholine. Six patients experienced an abrupt onset of symptoms during general anesthesia, and one during the post-anesthesia recovery period. One patient, a 33-year-old male undergoing an 11-hour retroperitoneal mass resection, exhibited a gradual onset of hypercarbia, hyperthermia and metabolic acidosis over 24 postoperative hours. Prior to surgery he was treated for depression with sertraline, and intraoperatively received fentanyl, so initially his clinical picture was attributed to serotonin syndrome and was given cyproheptadine. However, persistent fever led to empirical treatment with dantrolene, resulting in clinical improvement. Subsequent genetic testing confirmed a mutation in the *RYR1* gene. Another was a 38-year-old male undergoing uneventful orthopedic operation for six hours with sevoflurane. During emergence he developed profound muscle rigidity and began hyperventilating with tidal volumes exceeding 1 L, and a minute ventilation exceeding 20 L/min without elevated end-tidal carbon dioxide ($EtCO_2$). Arterial blood gas had pH (7.14), $PaCO_2$ 53 mmHg, base excess -10 mmol/L. He received 2.5 mg/kg IV dantrolene and a subsequent arterial blood gas, 90 minutes later, resulted as follows: pH 7.50, $PaCO_2$ 27 mmHg and base excess -2 mmol/L. He remained afebrile, his maximum serum creatine kinase (CK_{max}) was 796 U/L. Finally, a 60-year-old man undergoing carotid endarterectomy (patient # 5 in Table 1) developed gradual onset of hypercarbia relatively early during the anesthetic, but this went unrecognized and, instead of identifying MH, attempts were made to compensate for the rising $EtCO_2$ by increasing minute ventilation.

Dantrolene administration in MH suspected cases

Of the additional eight cases (Table 2) in which MH was initially suspected and dantrolene was administered, five were attributed to sepsis and/or multiorgan failure. Notably, all these MH-like events occurred in the perioperative setting and involved exposure to volatile agents. Two cases were associated with the use of multiple serotonergic medications and were subsequently diagnosed with serotonin toxicity. The remaining case involved a 45-year-old male who underwent cardiac surgery and developed persistent fever 24 hours postoperatively. In the absence of acidosis, MH was considered unlikely but dantrolene was administered empirically.

Oral dantrolene administration in NMS cases

There were two cases where oral dantrolene was used to treat suspected NMS. One was a 73-year-old female with altered mental status who developed rigidity and fever (40.0°C) following haloperidol administration for agitation. Laboratory findings were as follows: pH 7.42, $PaCO_2$ 23 mmHg, BE -9 mmol/L, CK_{max} 633 U/L. She responded well to dantrolene and hydration and had a full recovery. The second patient was a 78-year-old female hospitalized for altered mental status. On hospital day six following paliperidone administration, she developed worsening sensorium, hypercarbic respiratory failure, and fever (38.8°C) and had the following laboratory findings: pH 7.39, $PaCO_2$ 50 mmHg, BE +5 mmol/L, K 3.8 mmol/L, CK_{max} 86 U/L. Dantrolene was empirically administered for potential NMS but she did not improve and was ultimately diagnosed with toxic encephalopathy. She died 35 days later.

Dantrolene IV use in conditions unrelated to MH

The Supplementary Table 1 summarizes 14 patients who received IV dantrolene where a diagnosis of MH was never entertained. Nine of these patients were suspected of having NMS, of which eight were confirmed NMS cases. The ninth case was a 37-year-old female admitted with unresponsiveness and high fever; she was empirically treated with both cyproheptadine and dantrolene but was ultimately diagnosed with bacterial meningitis and died. Three patients received dantrolene for symptomatic treatment of muscle rigidity: a 44-year-old male with muscle rigidity secondary to catatonia, a 13-

year-old male with trismus secondary to juvenile dermatomyositis; and a 24-year-old-woman with episodic dystonia from anti-NMDA receptor autoimmune encephalitis secondary to an ovarian teratoma. There was a case where chronic oral dantrolene was substituted for the intravenous formulation. This patient was a 63-year-old male with cerebral palsy with spasticity who developed pneumonia and sepsis and required intubated and mechanical ventilation. The last patient was a 19-year-old male who developed central fever secondary to polytrauma who was administered oral bromocriptine for central dysautonomia. During hospitalization, he underwent an abdominal operation, and antipyretic management was subsequently transitioned to IV dantrolene.

DISCUSSION

Dantrolene use was uncommon in our clinical practice. When administered orally, dantrolene is primarily used to treat spasticity. When IV dantrolene is administered in the surgical setting, it was typically reserved for suspected MH cases, where treatment is warranted even with low suspicion due to the risk of death. Among the 17 patients who received IV dantrolene perioperatively, nine were confirmed to have MH. Notably, four of these nine patients had previously undergone uneventful general volatile anesthesia; of the four who underwent genetic testing all were found to carry a *RYR1* variant associated with MH susceptibility. This observation underscores that a history of uneventful exposure to triggering agents does not exclude MH susceptibility. The estimated prevalence of MH in our surgical population was 1 in 98,347 general anesthetics, consistent with previous reports [5, 6].

Characterizing patients who received IV dantrolene: Insights into MH and MH-like events

Among the clinically confirmed MH cases, five exhibited classic features, including an intraoperative rise in $EtCO_2$ and other hypermetabolic signs. In anesthetized patients, a rising $EtCO_2$ is often the earliest and most sensitive clinical indicator of MH (see Figure). However, MH can present atypically. In our series, one notable case involved a 3-month-old infant who developed severe hypercapnia and acidosis minutes

after induction of anesthesia in the absence of fever or hyperkalemia. This aligns with report from the Malignant Hyperthermia Association of the United States (MHAUS) Registry [7] which states that the youngest patients are less likely to exhibit fever and hyperkalemia as presenting part of the MH complex. Another patient developed MH-like symptoms during emergence from anesthesia which was initially attributed to serotonin syndrome; however, due to persistent fever, dantrolene was administered empirically with resolution of fever. Subsequent genetic testing confirmed susceptibility to MH. In the operative setting, a progressive and gradual rise in $EtCO_2$, particularly when repeated ventilatory adjustments (increase in tidal volume and/or respiratory rate), are needed to maintain normocapnia, should raise early suspicion for MH. However, MH may not be recognized until severe clinical signs become apparent (see Figure and Supplementary Figure 1). These cases highlight the importance of maintaining a high index of suspicion for MH, even when clinical signs are subtle, atypical, or even arise outside the intraoperative period.

A subset of our patients received IV dantrolene for suspected NMS or other refractory febrile conditions (Supplementary Table 1). Although dantrolene is not a first-line therapy for NMS, its use may be appropriate in cases complicated by substantial muscle rigidity and markedly elevated creatine kinase levels. Among the nine (eight treated with IV and one with PO dantrolene) patients ultimately diagnosed with NMS, eight presented with fever, and all had elevated creatine kinase concentrations. Additionally, one patient had refractory fever due to central dysautonomia following neurotrauma; he was treated with IV dantrolene, which resulted in resolution of the fever. There were an additional four patients who received IV dantrolene for muscle rigidity due to other disorders.

The role of genetic variants in shaping MH phenotypic expression

Four of our patients were found to carry *RYR1* gene variants associated with MH susceptibility. All were heterozygous, which may partially explain their relatively mild(er) clinical presentations. It is well established that the severity of *RYR1*-related myopathy depends on the specific genetic variant involved, reflecting a clear genotype-phenotype correlation [8-12]. Patients with heterozygous *RYR1* mutations may be expected to

exhibit milder clinical features compared to those with homozygous mutations [13]. However, interpretation of genetic testing remains complex, as the majority of MH cases reported in the literature also involve heterozygous *RYR1* variants [8, 14]. Homozygous variants have been reported in two patients with the Cys35Arg substitution and in one patient with the Arg614Cys substitution [11, 14, 15]. Regardless of zygosity, any patient testing positive for an MH-associated gene variant should be managed with extreme perioperative caution.

Using dantrolene administration as a surrogate marker for MH prevalence

Research into the incidence or prevalence of rare diseases such as MH presents notable methodological challenges. In response, collaborative registries involving government health agencies, academia, industry, and advocacy groups, such as MHAUS [7], have emerged to collect data from affected individuals. Automated analysis of large electronic healthcare databases offers a complementary approach to estimating the frequency of rare disorders [16-18]. In our cohort, perioperative IV dantrolene use was associated with MH diagnosis in 53% of cases presenting with MH-like symptomatology, supporting its potential utility as a marker for identification of patients with clinical presentation consistent with MH. Estimating the prevalence of adverse clinical events based on the administration of event-specific medications has precedent in perioperative research. For example, postoperative naloxone administration has been used as a surrogate marker for opioid-induced respiratory depression [19], and the use of rescue antiemetics has served as a proxy for identifying the incidence of postoperative nausea and vomiting [20]. However, unlike the cases described above, dantrolene is not used exclusively for MH; it has multiple clinical indications. Therefore, using dantrolene administration as a surrogate marker for MH necessitates careful review of the medical record to determine the specific clinical context, such as exposure to known triggering anesthetics and the rationale for its use. Moreover, relying on IV dantrolene administration as an indicator of emerging MH likely has low sensitivity and may fail to capture mild or atypical cases. For example, we recently encountered a patient who developed mild masseter spasm on induction of anesthesia with propofol and succinylcholine [21]. Anesthetic course with total intravenous anesthesia was entirely unremarkable; however, this patient developed severe rhabdomyolysis immediately

postoperatively, with no other MH-related signs, and he did not receive dantrolene. Subsequently he underwent whole-genome sequencing which revealed a heterozygous variant in the RYR1 gene (c.1840C>T), consistent with MH susceptibility. This highlights the notion that atypical (or mild) MH presentations may remain unrecognized and therefore not treated, and this will lead to an underestimation of MH prevalence when dantrolene administration is used as the surrogate marker for MH diagnosis [18].

Limitations

This study is subject to the inherent limitations of a retrospective design. MH is a potentially elusive disorder with a wide spectrum of clinical presentations, ranging from mild to fulminant and from typical to atypical manifestations, making early recognition and treatment challenging. Notably, milder or atypical episodes of MH may go unrecognized and will likely be managed without dantrolene, leading to an underestimation of MH prevalence when dantrolene administration is used as a proxy for MH episodes. Additionally, because MH cases were identified based on dantrolene use, there is a possibility that ambulatory surgical patients may have experienced MH after hospital discharge. However, it is likely that patients with serious reactions would have required prompt readmission, in which case they would be captured through our pharmacy records. Nevertheless, there remains the possibility that patients with mild clinical presentations did not seek further medical attention or did so at another medical facility and were therefore not captured in our dataset.

CONCLUSION

Dantrolene use was uncommon in our hospitalized population. Oral doses were mainly for chronic spasticity, while perioperative IV use was more often linked to suspected malignant hyperthermia (MH). However, specificity was low, since dantrolene was also given for conditions like NMS or serotonin syndrome. The estimated MH prevalence was approximately 1 in 100,000 anesthetic exposures, though this is likely an underestimate, as mild or atypical cases may go unrecognized. Our findings also reaffirm that a history of uneventful anesthesia does not rule out MH susceptibility.

ACKNOWLEDGEMENTS

We would like to acknowledge Anesthesia Clinical Research Unit (ACRU) Data Specialists, Ms. Xai Khang, RRT, LRT and Ms. Brianna Gilbertson, MSN, RN, for their help with data extraction.

Conflicts of interest: T.N.W. has received consulting fees from Merck & Co, Takeda Pharmaceuticals International Co, and Trevena, Inc.

Funding: This study was supported by the Department of Anesthesiology and Perioperative Medicine, Mayo Clinic. No external funding was provided.

Submitted: October 9, 2025

Accepted: November 7, 2025

Published online: November 17, 2025

REFERENCES

1. Alvarellos ML, Krauss RM, Wilke RA, Altman RB, Klein TE. PharmGKB summary: very important pharmacogene information for RYR1. Pharmacogenet Genomics. 2016;26(3):138-44. https://doi.org/10.1097/FPC.0000000000000198.

2. Caroff SN, Roberts CB, Rosenberg H, Tobin JR, Watt S, Mashman D, et al. Intravenous dantrolene in hypermetabolic syndromes: a survey of the U.S. Veterans Health Administration database. BMC Anesthesiol. 2022;22(1):298. https://doi.org/10.1186/s12871-022-01841-z.

3. Pawar S, Rosenberg H, Adamson R, LaRosa J, Chamberlain R. Dantrolene in the Treatment of Refractory Hyperthermic Conditions in Critical Care: A Multicenter Retrospective Study. OJAnes. 2015;5:63-71. https://doi.org/10.4236/ojanes.2015.54013.

4. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495-9. https://doi.org/10.1016/j.ijsu.2014.07.013.

5. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001-2005. Anesth Analg. 2009;109(4):1162-6. https://doi.org/10.1213/ane.0b013e3181ac1548.

6. Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology. 2009;110(1):89-94. https://doi.org/10.1097/ALN.0b013e318190bb08.

7. Salazar JH, Yang J, Shen L, Abdullah F, Kim TW. Pediatric malignant hyperthermia: risk factors, morbidity, and mortality identified from the Nationwide Inpatient Sample and Kids' Inpatient Database. Paediatr Anaesth. 2014;24(12):1212-6. https://doi.org/10.1111/pan.12466.

8. McCarthy TV, Quane KA, Lynch PJ. Ryanodine receptor mutations in malignant hyperthermia and central core disease. Hum Mutat. 2000;15(5):410-7. https://doi.org/10.1002/(SICI)1098-1004(200005)15:5<410::AID-HUMU2>3.0.CO;2-D.

9. Gillard EF, Otsu K, Fujii J, Khanna VK, de Leon S, Derdemezi J, et al. A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative

of human malignant hyperthermia. Genomics. 1991;11(3):751-5. https://doi.org/10.1016/0888-7543(91)90084-r.

10. Iles DE, Lehmann-Horn F, Scherer SW, Tsui LC, Olde Weghuis D, Suijkerbuijk RF, et al. Localization of the gene encoding the alpha 2/delta-subunits of the L-type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. Hum Mol Genet. 1994;3(6):969-75. https://doi.org/10.1093/hmg/3.6.969.

11. Deufel T, Sudbrak R, Feist Y, Rubsam B, Du Chesne I, Schafer KL, et al. Discordance, in a malignant hyperthermia pedigree, between in vitro contracture-test phenotypes and haplotypes for the MHS1 region on chromosome 19q12-13.2, comprising the C1840T transition in the RYR1 gene. Am J Hum Genet. 1995;56(6):1334-42. PMID: 7762556.

12. Serfas KD, Bose D, Patel L, Wrogemann K, Phillips MS, MacLennan DH, et al. Comparison of the segregation of the RYR1 C1840T mutation with segregation of the caffeine/halothane contracture test results for malignant hyperthermia susceptibility in a large Manitoba Mennonite family. Anesthesiology. 1996;84(2):322-9. https://doi.org/10.1097/00000542-199602000-00009.

13. Pandey R, Chandratre S, Roberts A, Dwyer JS, Sewry C, Quinlivan R. Central core myopathy with RYR1 mutation masks 5q spinal muscular atrophy. Eur J Paediatr Neurol. 2011;15(1):70-3. https://doi.org/10.1016/j.ejpn.2010.04.003.

14. Rueffert H, Olthoff D, Deutrich C, Thamm B, Froster UG. Homozygous and heterozygous Arg614Cys mutations (1840C-->T) in the ryanodine receptor gene co-segregate with malignant hyperthermia susceptibility in a German family. Br J Anaesth. 2001;87(2):240-5. https://doi.org/10.1093/bja/87.2.240.

15. Lynch PJ, Krivosic-Horber R, Reyford H, Monnier N, Quane K, Adnet P, et al. Identification of heterozygous and homozygous individuals with the novel RYR1 mutation Cys35Arg in a large kindred. Anesthesiology. 1997;86(3):620-6. https://doi.org/10.1097/00000542-199703000-00014.

16. Kariampuzha WZ, Alyea G, Qu S, Sanjak J, Mathe E, Sid E, et al. Precision information extraction for rare disease epidemiology at scale. J Transl Med. 2023;21(1):157. https://doi.org/10.1186/s12967-023-04011-y.

17. Taruscio D, Gahl WA. Rare diseases: challenges and opportunities for research and public health. Nat Rev Dis Primers. 2024;10(1):13. https://doi.org/10.1038/s41572-024-00505-1.

18. Pinyavat T, Rosenberg H, Lang BH, Wong CA, Riazi S, Brady JE, et al. Accuracy of malignant hyperthermia diagnoses in hospital discharge records. Anesthesiology. 2015;122(1):55-63. https://doi.org/10.1097/ALN.0000000000000467.

19. Valencia Morales DJ, Laporta ML, Meehan AM, Schroeder DR, Sprung J, Weingarten TN. Incidence and Outcomes of Life-Threatening Events During Hospitalization: A Retrospective Study of Patients Treated with Naloxone. Pain Med. 2022;23(5):878-86. https://doi.org/10.1093/pm/pnab310.

20. Sprung J, Deljou A, Schroeder DR, Warner DO, Weingarten TN. Effect of Propofol Infusion on Need for Rescue Antiemetics in Postanesthesia Care Unit After Volatile Anesthesia: A Retrospective Cohort Study. Anesth Analg. 2024;139(1):26-34. https://doi.org/10.1213/ANE.0000000000006906.

21. Harrison TE, Weingarten TN, Sprung J. Succinylcholine-induced rhabdomyolysis in a patient with RYR1 and BCHE variants: A case report. Biomol Biomed. 2025. https://doi.org/10.17305/bb.2025.13435

TABLES AND FIGURES WITH LEGENDS

Table 1. Use of dantrolene in hospitalized patients with suspected malignant hyperthermia

Age Sex	Procedure Triggering agents	Clinical course, therapies, outcomes	MH diagnosis Genetic testing and/or clinical
20 F	Oral cyst excision SUX, DES	Masseter spasm with induction, unremarkable anesthetic course for 1-h procedure. During emergence increase in $EtCO_2$ 55 mmHg with respiratory rate to 50 per minute. pH 7.32, $PaCO_2$ 43 mmHg, BE -4 mmol/L, K 4.1 mmol/L. Remained afebrile. Dantrolene (2.5 mg/kg during surgery) administration, hydration. Complaint of lower extremity muscle soreness several hours. CK_{max} 11,502 U/L. Full recovery. Past Anest Hx, *n*=13: ASD repair (ISO); Liver Tx x2 (ISO, SUX); GI procedures x6 (SEVO, DES); Pectus excavatum repair (ISO); Minor procedures x3 (SEVO).	MH – confirmed Heterozygous RYR1 mutation c.7354C>T (p.Arg2452Trp)
12 M	Cardiac catheterization SEVO	90 min after induction abrupt development of fever (38.8 °C), $EtCO_2$ 74 mmHg, pH 7.16, $PaCO_2$ 76 mmHg, BE -7 mmol/L, K 6.3 mmol/L. Non-triggering anesthetic, dantrolene (2.5 mg/kg during surgery followed by 24-hour infusion), cooling, hydration. Vital signs normalized. Remained intubated for 24 hours. CK_{max}	MH – confirmed Heterozygous RYR1 mutation c.6617C>T (p.Thr2206Met)

		538 U/L, urine myoglobin 30 mcg/L. Full recovery. Past Anest Hx *n*=4: Heart operations x2 (ISO, SEVO); Minor procedures x2 (ISO, SEVO).	
7 M	Tympanomastoidectomy SEVO	5-h after induction rapid development of tachycardia (HR 170), tachypnea, hypotension, fever (39.0 °C), $EtCO_2$ 100 mmHg, pH 7.04, $PaCO_2$ 78 mmHg, BE -9 mmol/L, K 6.6 mmol/L. Non-triggering anesthetic, dantrolene (five 2.0 mg/kg doses over 1 hour during surgery), cooling, hydration. Vital signs normalized. CK_{max} 6,694 U/L, lactate 6.3 mmol/L, urine myoglobin 64 mcg/L. Full recovery. Past Anesth Hx, *n*=2: Tympanostomy (SEVO); Myringotomy (SEVO)	MH – confirmed Heterozygous RYR1 mutation c.7300G>A
33 M	Retroperitoneal mass resection ISO Serotonergic medications: cannabis, sertraline, fentanyl	Gradual increase in temperature (38.4°C) and $EtCO_2$ 53 mmHg over 11-h surgery with intraoperative pH 7.24, $PaCO_2$ 51 mmHg, BE -6 mmol/L. Initial diagnosis was serotonin syndrome treated with cooling, cyproheptadine. Because of persistent fevers (39.5 °C) dantrolene administered 24-h after surgery (100 mg doses every 5 hours for 3 doses). At time of dantrolene administration pH 7.32, $PaCO_2$ 55 mmHg, BE -6 mmol/L. CK_{max} 32,910 U/L, lactate, K 6.1 mmol/L, urine myoglobin 850 mcg/L, ALT 235 U/L, AST 865 U/L. Full recovery. Past Anesth Hx:	MH – confirmed Heterozygous RYRI mutation c.6617 C>T (p.Thr2206Met)

		TIVA x2	
60 M	Carotid endarterectomy SUX, ISO	3-h after induction rapid increase in $EtCO_2$ 100 mmHg, temp 40.8 °C, pH 7.14, $PaCO_2$ 80 mmHg, BE -2 mmol/L, K 6.0 mmol/L. Non-triggering anesthetic, dantrolene (150 mg during surgery), cooling with temp and $EtCO_2$ normalizing < 30 min, hydration. CK_{max} 3,544 U/L, urine myoglobin 378 mcg/L. Full recovery within 24 hours. Past Anesth Hx: TIVA x1	MH – confirmed
74 F	Lumbar spine surgery SUX, ISO	Unremarkable for 6-h case. PACU: severe full body muscle rigidity, fever (39.4 °C), SpO_2 88%, tachypneic, mental status changes, pH 7.08, $PaCO_2$ 82 mmHg, BE -6 mmol/L, K 4.9 mmol/L, CK_{max} 1,095U/L. Dantrolene (220 mg during surgery, 70 mg every 6 hours for 24 hours), cooling, hydration. Intubated for 24-h with full recovery. Past Anesth Hx: No	MH – confirmed
61 F	Breast surgery SUX, ISO	2-h after induction rapid increase in $EtCO_2$ 61 mmHg, fever (38.4 °C), pH 7.25, $PaCO_2$ 59 mmHg, BE -2 mmol/L, K 6.0 mmol/L. Surgery terminated, dantrolene (180 mg during surgery, 100 mg IV every 6 hours for 24 hours, followed by 100 mg oral every 8 hours for 3 days), cooling, hydration. CK_{max} 5,962 U/L, urine myoglobin 1,250 mcg/L. Full recovery. Past Anesth Hx: No	MH – confirmed

3-month F	MRI SEVO, ISO	Induction with SEVO switched to ISO. With 6 min rapid increase in $EtCO_2$ 89 mmHg. Non-triggering anesthetic, dantrolene (10 mg during procedure), hydration. T_{max} (36.7°C), pH 7.07, $PaCO_2$ 72 mmHg, BE -9 mmol/L, K 4.0 mmol/L. Full recovery. Past Anesth Hx: No	MH – confirmed
38 M	Hip arthroscopy SEVO	During emergence after a 6-hour surgery: muscle rigidity, tachycardia, afebrile, metabolic acidosis: pH 7.14, $PaCO_2$ 53 mmHg, BE -10 mmol/L, K 4.9 mmol/L. Dantrolene (2.5 mg/kg during surgery), hydration, reintubated/mechanical ventilation. CK_{max} 796 U/L. Full recovery. Past Anesth Hx: Arthroscopy x2 (SUX, SEVO, ISO); Laminectomy (SUX, SEVO, ISO).	MH – confirmed

Abbreviations: M: Male; F: Female; MH: Malignant hyperthermia; SUX: Succinylcholine; DES: Desflurane; EtCO2: End-tidal carbon dioxide; BE: Base excess; CK_{max}: Maximum creatine kinase; RYR1: Ryanodine receptor type 1; SEVO: Sevoflurane; ISO: Isoflurane; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PACU: Postanesthesia care unit; MRI: Magnetic resonance imaging; NMS: Neuroleptic malignant syndrome; ECT: Electroconvulsive therapy; TIVA: Total intravenous anesthesia; Past Anest Hx: Indicates exposure to general anesthesia before currently reported events. Reference values: CK, reference, 39-308 U/L; ALT, reference, 7-55 U/L; AST, reference, 8-48 U/L; Urine myoglobin, reference, ≤65 mg/L.

Table 2. Hospitalized patients treated with dantrolene for suspected malignant hyperthermia later diagnosed with alternative conditions

Age Sex	Procedure Triggering agents	Clinical course, therapies, outcomes	Final diagnosis
63 F	Cardiac surgery SUX, ISO Serotonergic medications: methylene blue, sufentanil, omeprazole, venlafaxine	8-h after surgery in ICU developed respiratory acidosis, fever, ectopy, hyperdynamic cardiac index (11 LPM), muscle rigidity, pH 7.24, $PaCO_2$ 55 mmHg, BE -4 mmol/L, K 6.4 mmol/L. Dantrolene, cooling, diuresis with resolution of symptoms within 6 hours. CK_{max} 2,179 U/L. Full recovery except perioperative stroke.	Final diagnosis not established, either serotonin syndrome or NMS
45 M	Cardiac surgery ISO	Persistent fever (39.7°C) for 24-h after surgery, pH 7.39, $PaCO_2$ 47 mmHg, BE +3 mmol/L, CK_{max} 1,625 U/L, K 6.1 mmol/L. Empiric dantrolene, cooling. Full recovery.	Final diagnosis not established
88 F	ECT, SUX Serotonergic meds: fluoxetine, omeprazole	After ECT became rigid, febrile (39.2°C), pH 7.46, $PaCO_2$ 35 mmHg, BE +1 mmol/L. Empiric dantrolene, cooling, cyproheptadine. CK_{max} 47 U/L. Full recovery.	Final diagnosis not established, either serotonin syndrome or NMS
39 M	Cardiac transplant,	Day of surgery in ICU developed fever (41.7°C) diffuse shivering, pH 7.37,	Sepsis and multiorgan

	ISO, SUX	$PaCO_2$ 47 mmHg, BE +1 mmol/L. 14-h after surgery, dantrolene empirically initiated. The fever resolved within 24 hours.	failure
65 F	Total hip arthroplasty SEVO, SUX	6-h after surgery developed tachypnea, hypotension, diaphoresis, fever (40°C). pH 6.98, $PaCO_2$ 22 mmHg, BE -26 mmol/L, lactate 16 mmol/L, CK_{max} 235 U/L, urine myoglobin > 5000 mcg/L, AST 22,620 U/L, INR 7.9. Empiric dantrolene without improvement. Died postoperative day 2 of multiorgan failure.	Sepsis and multiorgan failure
66 M	Cardiac surgery Non-triggering anesthetic	Had chronically elevated CK, so non-trigger anesthetic was used. 8-h after surgery became febrile (39.3°C). pH 7.24, $PaCO_2$ 44 mmHg, BE -8 mmol/L, K 4.2 mmol/L. Administered dantrolene with resolution of fever. CK_{max} 1,545 U/L. Positive blood cultures, given antibiotics. Full recovery.	Sepsis
61 Y	Abdominal exploration ISO	Aortic root replacement for infective endocarditis. Next day an emergent abdominal exploration underwent. He had fever (41.0 °C), pH 7.33, $PaCO_2$ 38 mmHg, BE -6 mmol/L, K 6.5 mmol/L. Empiric dantrolene administered though suspicion of MH was low. No clinical improvement. Died two days later of multiorgan failure.	Sepsis

53 M	Intubated for hemodynamic instability SUX	Hospitalized for dysrhythmia and ICD discharge in setting congenital heart disease and acute heart failure. Intubated on hospital day 1 for hemodynamic instability with SUX. Developed fever (40.9°C) and was administered single dose dantrolene without improvement. pH 7.35, $PaCO_2$ 42 mmHg, BE -2 mmol/L, K 4.7 mmol/L, CK_{max} 194 U/L, urine myoglobin 68 mcg/L. Died hospital day 8 from sepsis and multiorgan failure.	Sepsis

Abbreviations: M: Male; F: Female; MH: Malignant hyperthermia; SUX: Succinylcholine; $EtCO_2$: End-tidal carbon dioxide; BE: Base excess; CKmax: Maximum creatine kinase; SEVO: Sevoflurane; ISO: Isoflurane; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ICD: Internal cardiac defibrillator; PACU: Postanesthesia care unit; MRI: Magnetic resonance imaging; NMS: Neuroleptic malignant syndrome; ECT: Electroconvulsive therapy. Reference values: CK, reference, 39-308 U/L; ALT, reference, 7-55 U/L; AST, reference, 8-48 U/L; Urine myoglobin, reference, ≤65 mg/L; Serum lactate, reference 0.60-2.30 mmol/L.

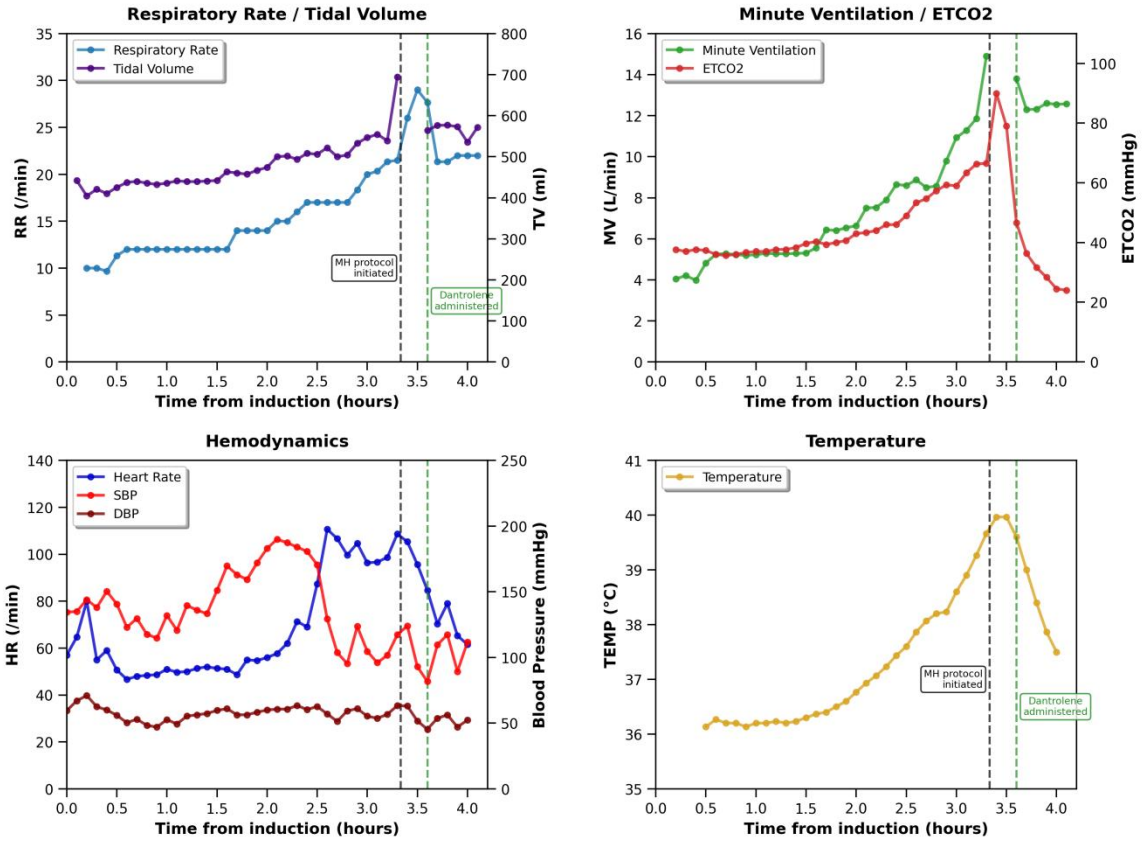

Figure 1. Intraoperative hemodynamic, respiratory, and temperature changes in a 60-year-old man undergoing carotid endarterectomy. This graphical representation depicts the gradual onset of malignant hyperthermia (MH) during anesthesia. An early intraoperative indicator of MH, particularly the rising end-tidal carbon dioxide ($EtCO_2$), was initially obscured as the increasing $EtCO_2$ levels were mitigated by augmenting minute ventilation. A full-blown MH crisis became evident only toward the conclusion of the procedure, characterized by severe hypercapnia ($EtCO_2$ 100 mmHg, $PaCO_2$ 88 mmHg), respiratory acidosis (pH 7.14), hyperkalemia (serum potassium 6.0 mmol/L), and hyperthermia (temperature 40.8 °C). This was followed by hemodynamic instability, transitioning from hypertension and tachycardia to hypotension. At that point MH was suspected, prompting the cessation of triggering agents, intravenous administration of dantrolene, and the initiation of active cooling measures. Both $EtCO_2$ and temperature normalized within 30 minutes following treatment.

SUPPLEMENTAL DATA

Supplemental data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/13340/4047